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EXAMINER

KAPUSHOC, STEPHEN THOMAS

ART UNIT	PAPER NUMBER
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1634

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,973	ZHAO ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 January 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 10-13, 25-28 and 32-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7, 8, 14-19, 21-23 and 29-31 is/are rejected.
- 7) ☒ Claim(s) 4, 6, 9, 18, 20 and 24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 March 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>7/30/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-41 are pending.

Applicant's election with traverse of Group I, claims 1-31, filed on Jan. 27, 2006, is acknowledged. Applicant's further election of the AHASL1D gene and the primer pair of SEQ ID NOs: 5 and 7, is also acknowledged.

Claims 10-13, 1,25-28 and 32-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-9, 14-24, and 29-31 are examined on the merits.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-31 in the reply filed on Jan. 27, 2006 is acknowledged. The traversal is on the ground(s) that of the claims of group II, only claim 32 is drawn to nucleic acids *per se*. This is not found persuasive because claims 33-41 are drawn to kits comprising nucleic acids; such claims are classifiable in class 536, subclass 23.1; and such kits can be used for purposes other than the detection of mutant wheat alleles.

2. Applicant's further election with traverse of the AHASL1D gene and the primer pair of SEQ ID NOs: 5 and 7 in the reply filed on Jan. 27, 2006 is acknowledged. The traversal is on the ground(s) that the various AHASL genes are similar, and a search of one gene would be coextensive with a search of all the genes. This is not found persuasive because a search of any particular sequence cannot in fact be known to be coextensive with the search of another different sequence prior to actually performing the search. Additionally, the degree of similarity of the entire length of the AHASL genes cannot be considered indicative of a search of the claimed primers, which are

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shorter, and the instant application asserts that the primers are at least different enough to discriminate between the different AHASL genes via PCR amplification.

The requirement is still deemed proper and is therefore made FINAL.

Sequence Compliance

2. This application, 10/805,973, contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below:

The application contains sequences that are not identified by SEQ ID NOs and are not contained in the sequence listing of the application. For example, the description of Figure 1C (p.9 lns.17-20) references SEQ ID NOs 19-21, however the sequence listing only contains 18 sequences (<160> 18). Additionally, Figures 3 and 4 contain the nucleic acid sequences of AHAS1B, AHASL1D, and AHASL1A, however the sequences are not identified by a SEQ ID NO, nor are the sequences part of the sequence listing of the application.

3. In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, as appropriate, a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, and a letter stating that the content of the paper and computer readable

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copies are the same. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned.

Specification

4. The disclosure is objected to because of the following informalities: The description of Figure 1C does not accurately reflect the sequences contained in the figure. The description indicates that the figure depicts the nucleotide sequence of the wild-type AHASL1A gene (SEQ ID NO: 18), however SEQ ID NO: 18 in the sequence listing appears to be the mutant form of AHASL1A.

Appropriate correction is required.

Drawings

5. The drawings are objected to because:

The primer sequences for several of the primers (CM-F, CM-R, 1A,D-F, 1B-R, 1D-R, 1B-R, 1A-R) indicated on Figures 3 and 4 do not match the sequences of these primers as identified in the sequence listing. For example, p.10 of the specification (ln.29) indicates that SEQ ID NO: 1 is a forward AHASL primer also referred to as CM-F; the sequence listing shows SEQ ID NO: 1, <223> Primer CM-F, as a sequence 21 nucleotides in length (<211> 21), but sheet 1 of Figure 3 appears to indicate only 20

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nucleotides of sequence for this primer. Additionally, the appropriate identifying SEQ ID NO should accompany each sequence in Figures 3 and 4 in the description of the figures and/or within the figures.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1, 7, 8, 14, 15, 21-23, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hucl et al (2003) (WO 03/014357) in view of DelRio-LaFreniere et al (2001).

Hucl et al teaches the molecular basis of imidazolinone resistance in wheat plants. The reference teaches that resistance to imidazolinone can be conferred by a guanine to adenine substitution in the AHASL1 gene (referred to in Hucl et al as Asl1), which results in a serine to asparagine substitution (p.7 Ins. 1-15; Figure 8 page 17/42; p.13 Ins 2-3; Figure 13). Hucl teaches the nucleic acid and deduced amino acid sequences of the AHSAL1 genes of several imidazolinone resistant wheat plants (Fig 8) including the mutation responsible for herbicide resistance. The reference teaches that imidazolinone resistant mutant alleles can be detected by amplifying AHASL1 genes and comparing the amplified gene sequence to that of a known wild-type control (p.17 ln.33-p.18 ln.13; p.20 ln.26-p.21 ln.2). Relevant to step (a) of claim 1, the reference teaches the use of genomic DNA (p.18 ln.11). Relevant to step (b) of claim 1, Hucl et al teaches the portion of the AHASL1 nucleic acid sequence that is responsible for the imidazolinone resistance-mutation, including nucleotides 3-23 of SEQ ID NO: 12 of the instant application (for example see Fig 8, p17/42 of the figures, (SEQ ID NO: 15) the nucleotides encoding the amino acid sequence HVLPMIP(N/S) beginning at amino acid 620).

Regarding claim 7, Hucl et al teaches the AHASL1 nucleic acid sequence that includes the sequence relevant to SEQ ID NO: 3 of the instant application (for example

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see Fig 8, p14/42 of the figures, row 4 (SEQ ID NO: 15) the nucleotides encoding amino acids GEAlIA, beginning at amino acid 451).

Regarding claim 8, Hucl teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant (p.9 Ins. 25-33), and teaches the sequence of the *Imi1* wheat gene (Fig 8; p.7 Ins.1-15), which is the AHASL1D gene on the D genome, as evidenced by Pozniak et al (2004) (p.1439 – Chromosome location of AHAS genes).

Regarding claims 15, 21, and 23, the teachings of Hucl et al ~~are applied to~~ ~~are applied to~~ are applied to steps (a), (b), and (d) of claim 15 as they were applied to claims 1, 7 and 8 earlier in this rejection. Additionally, Relevant to step (c) of claim 15, Hucl et al teaches the wild-type AHASL1 nucleic acid sequence that is responsible for imidazolinone sensitivity, including the sequence relevant to SEQ ID NO: 10 of the instant application (for example see Fig 8, p17/42 of the figures, (SEQ ID NO: 21) nucleotides that encode amino acids 621-633, HVLPMIPSGGAFKD).

Regarding claim 21, Hucl et al teaches the AHASL1 nucleic acid sequence that includes the sequence relevant to SEQ ID NO: 3 of the instant application (for example see Fig 8, p14/42 of the figures, row 4 (SEQ ID NO: 15) the nucleotides encoding amino acids GEAlIA beginning at amino acid 451).

Regarding claim 22, Hucl teaches the AHASL1 nucleic acid sequence that includes the sequence relevant to SEQ ID NO: 4 of the instant application (for example see Fig 8, p17/42 of the figures, row 4 (SEQ ID NO: 15) nucleotides that encode amino acids 621-627, VLPMIP(N/S)).

Regarding claim 23, Hucl teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant (p.9 Ins. 25-33), and teaches the sequence of the *Imi1* wheat gene (Fig 8; p.7 Ins.1-15), which is the AHASL1D gene on the D genome, as evidenced by Pozniak et al (2004) (p.1439 – Chromosome location of AHAS genes).

Hucl does not teach the analysis of AHASL1 genes via allele specific PCR using oligonucleotide primers, or primers with mismatches as are required for primers directed to nucleotides 3 to 23 of SEQ ID NO: 12 with a cytidine at the 3' end (step (b) of claims 1 and 15, step (c) of claim 30).

DelRio-LaFreniere et al teaches a method for the detection of single nucleotide polymorphisms using allele-specific primers that contain additional intentional mismatches (p.201 – Methods and results; p.202, right col., last paragraph). Relevant to step (b) of claim 1, the reference teaches a PCR reaction comprised of genomic DNA from whole blood (p.203- DNA purification), dNTPs, a polymerase, forward and reverse gene specific primers (referred to in the reference as LS1 and LS2 (locus specific) primers), and a mutant-allele-specific primer (referred to in the reference as AS-MUT) (p.204-PCR setup conditions). The reference teaches that mutant and wild-type allele specific primers are designed to flank the polymorphic position (p.203 – Prothrombin mutation (factor II), FVL), and that additional mismatches within the primers can increase amplification specificity by making primers refractory to amplification of non-cognate alleles; the reference further indicates that the ideal nature (e.g. pyrimidine to pyrimidine or purine to purine) and locations (e.g. antepenultimate, pentultimate) of mismatches can be experimentally determined (p.202, right col., ln.46 – p.203, left col.,

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ln.9; Table 3; p.207, left col., lns.4-10). Relevant to step (c) of claim 1, DelRio-LaFreniere et al teaches the detection of PCR products using gel electrophoresis and ethidium bromide staining (p.204, right col., lns.8-11). DelRio-LaFreniere et al teaches that the allele specific primer is capable of annealing to a region of the analyzed gene that is nested between the annealing sites of the gene-specific primers (Fig. 1).

Regarding claims 14 and 29, DelRio-LaFreniere et al teaches the detection of PCR products using gel electrophoresis and ethidium bromide staining (p.204, right col., lns.8-11; Figs. 2, 4).

Relevant to step (c) of claim 15, DelRio-LaFreniere also teaches the use of wild-type allele-specific-primers for detection of wild-type alleles (Tables 1 and 3; Figure 1; p.202, right col., lns.15-18).

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the mutation detection methods of Hucl et al so as to have used the allele-specific amplification and primers designed with intentional mismatches primers of DelRio-LaFreniere et al. One would have been motivated to do so because of the teaching of DelRio-LaFreniere et al that indicate intentionally mismatched allele-specific amplification methods provide accurate results (p.205, right col., lns.22-31) and are simple to perform (p.201 – Methods and results), and further teaches that various intentional mismatches can be tested for optimum specificity (p.203, left col., lns.9-14; Table 3; p.207, left col., lns.16-25).

The combined methods would have necessarily included experimentation, as suggested by DelRio-LaFreniere et al (p.207, left col., lns.4-25), to select primers for

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mutation detection. Such experimentation would thus include creating the claimed oligonucleotides such as SEQ ID NOs: 3 and 4, and mutant-allele-specific primer nucleotide sequences that have cytidine at the 3' end and wild-type-allele-specific primer nucleotide sequences that have guanosine at the 3', or any other primers which contain 3' end and/or internal mismatches with regard to their cognate binding sites. It is noteworthy that claims that [REDACTED] encompass a variety of primers; for example, the mutant-allele-specific primer of claim 1 step (b) requires that the primer have 'a cytidine at the 3' end'. The claim does not require that the cytidine is at the 3' terminus, thus one may consider any primer with a cytidine at a position other than the 5' terminus as satisfying this claim limitation. Further, regarding the specific primers and binding sites listed in the claims, the selection of any primers within the sequence taught by Hucl et al, following the guidance given by DelRio-LaFreniere et al would have been prima facie obvious to one of skill in the art. One would have expected any primer from within this sequence to function within the methods taught by Hucl et al in view of DelRio-LaFreniere et al for the detection of the mutation taught by Hucl et al. Absent a secondary consideration, such as an unexpected result, the claimed invention is prima facie obvious.

8. Claims 2, 4, 5, 16, 18, 19, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hucl et al (2003) (WO 03/014357) in view of DelRio-LaFreniere et al (2001) and further in view of Stanton (2002) US Patent 6,475,736.

The teachings of Hucl et al in view of DelRio-LaFreniere et al are applied to claims 2, 4, 5, 16, 18, 19, and 30 as they were previously applied to claims 1, 7, 8, 14, 15, 21-23, and 29 earlier in this office action.

Hucl et al in view of DelRio-LaFreniere et al teaches a method for the detection of mutant AHASL alleles that confer tolerance to imidazolinone on a wheat plant. The method utilizes allele-specific primers with intentional mismatches for amplification, and uses mutant and wild-type specific primers.

Hucl et al in view of DelRio-LaFreniere et al does not teach a pre-amplification step using primers that amplify a product that contains nested annealing sites for the gene-specific primers used to detect specific mutations.

Stanton teaches methods for the analysis of DNA using amplification of polymorphic sites. Relevant to claims 2, 16, and 30 step (b), Stanton teaches that the PCR amplification step of a genotyping procedure can be modified to increase sensitivity by using nested PCR (two rounds of PCR, first with an outside set of primers, then with an inside set) (col.34 Ins.35-39).

Regarding claims 4 and 18, Hucl teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant (p.9 Ins. 25-33), and provides an alignment of the three different imidazolinone resistance genes (Fig. 12). The sequences taught by Hucl et al include primer binding sites for which it would be a necessary property that oligonucleotide primers directed to those regions would anneal to AHASL1a, AHASL1B, and AHASL1D.

Regarding claims 5 and 19, which depend from claims 2 and 16 respectively, Hucl teaches the AHASL1 sequence that includes the sequence relevant to SEQ ID NO: 1 of the instant application (for example see Fig 12, p39/42 of the figures, nucleotides 901-920).

Therefore it would have been prima facie obvious at the time the invention was made to have modified the mutation detection methods of Hucl et al in view of DelRio-LaFreniere et al so as to have incorporated a pre-amplification step as taught by Stanton. One would have been motivated to do so based on the teachings of Stanton that a pre-amplification step can increase the sensitivity of the methods (col 34 lns.36-37). One would have had a reasonable expectation of success because Stanton teaches the pre-amplification step in association with PCR based methods, and the allele detection methods of DelRio-LaFreniere et al are PCR based. Further regarding claims 5 and 19, it would be obvious to use primers comprising the claimed sequence (SEQ ID NO: 1) given the alignment of the three imidazolinone resistance genes (Fig. 12 of Hucl et al) and the consensus sequence that indicates this region is conserved among the three genes, as use of such a primer would allow for subsequent analysis of any of the three AHASL1 genes from any of the three wheat genomes.

9. Claims 3, 17, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hucl et al (2003) (WO 03/014357) in view of DelRio-LaFreniere et al (2001) and Stanton (2002) US Patent 6,475,736 and further in view of Werle et al (1994).

The teachings of Hucl et al in view of DelRio-LaFreniere et al and Stanton are applied to claims 3, 17, and 31 as they were previously applied to claims 2, 16, and 30 earlier in this office action.

Hucl et al in view of DelRio-LaFreniere et al and Stanton teaches a method for the detection of mutant AHASL alleles that confer tolerance to imidazolinone on a wheat plant. The method utilizes a pre-amplification step, followed by the use of allele-specific primers with intentional mismatches for amplification, and uses mutant and wild-type specific primers.

Hucl et al in view of DelRio-LaFreniere et al and Stanton does not teach the use of an exonuclease following the pre-amplification step.

Werle et al teaches the use of exonuclease I to degrade excess primers and nucleotides from PCR products prior to analysis by sequencing. Relevant to claims 3, 17, and 31, Werle et al teaches pre-amplification of a PCR product from genomic DNA, followed by treatment with exonuclease, then analysis of the exonuclease treated PCR product using the same conditions as for PCR of genomic DNA (p.4354, Ins.20-36).

Therefore it would have been prima facie obvious at the time the invention was made to have modified the mutation detection methods of Hucl et al in view of DelRio-LaFreniere et al and Stanton so as to have incorporated an exonuclease digestion step as taught by Werle et al. One would have been motivated to do so based on the teachings of Werle et al that exonuclease digestion removes factors that interfere with analyses that utilize PCR based methods (p.4354 In.13-16; p.4354 In.34-37), and that the exonuclease method is simple to use with minimum sample handling, risk of cross-

contamination and amount of DNA template required, and the method is reliable, convenient, and cost effective (p.4355 Ins.1-6). One would have had a reasonable expectation of success because Werle asserts that the method has broad applicability in mutational analysis by a PCR based method (p.4355 Ins.6-8), and the allele-specific amplification method of DelRio-LaFreniere et al is a PCR based method.

Conclusion - Claim Objections

10. Claims 6, 9, 20, and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Claims 6 and 20 require SEQ ID NO: 2, and claims 9 and 24 require SEQ ID NO: 7. The sequence of the 3' end (the portion of the gene downstream from the G→A (Ser→Asn) mutation site at position 1594 of the AHASL1D gene in Figure 4 of the instant application) of the AHASL1D gene from wheat was known in the prior art of GenBank entry BJ296872 (2002). The sequence of GenBank entry BJ296872 contains the binding sites for SEQ ID NO: 2 (the AHASL common reverse primer) and SEQ ID NO: 7 (the AHASL1D gene-specific reverse primer) as well as the mutation site and the sequence relevant to SEQ ID NOs 3 and 4 (the mutant- and wild-type -allele-specific primers, respectively). However, the sequence in GenBank entry BJ296872 is identified only as a wheat expressed sequence tag (EST) from a cDNA library of mRNA 3'-ends. The sequence is not identified as being a portion of the AHASL1D gene, and there is no teaching in the GenBank entry for one of skill in the art to use the sequence to design

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primers for the detection of a mutant allele that confers imidazolinone resistance.

Additionally, while the prior art of Hucl et al teaches that there are multiple wheat genomes (A, B, and D), each of which contains an AHAS gene of a particular sequence (p.9 Ins.23-33), the reference does not provide any particular motivation to use sequence additional to that provided in Figure 8 of Hucl et al for the design of primers for the detection of a mutant allele that confers imidazolinone resistance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Stephen Kapushoc
Art Unit 1634


JULIET C. SWITZER
PRIMARY EXAMINER